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(54) COMPOSITIONS CONTAINING HETEROCYCLIC BRONCHODILATING AGENTS

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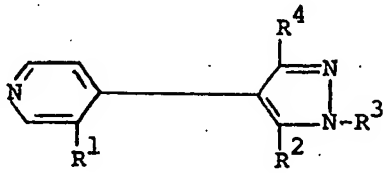
This invention is concerned with agents that effectively inhibit bronchial constriction and a method for treating animals to overcome bronchial constriction induced by histamine or other bronchial constricting substances. The agents found useful in the method and formulations of this invention have been found to be superior to most bronchodilating agents because they have relatively low chronotropic effect. Additionally, some of the compounds also exhibit useful hypotensive properties.

The agents useful in the method and formulations of this invention are 4-(4-pyridyl)pyrazole compounds which optionally can carry one or more of a variety of substituents in either or both of the heterocyclic nuclei. Products that have been found to be particularly effective have the structure



I

and pharmacologically acceptable salts thereof wherein R^1 represents hydrogen, nitro, amino, acetylamino, mono- or di-alkylamino, cyano, phenyl, hydroxy, alkoxy, or halo, preferably chloro; R^2 represents hydrogen, halogen, preferably chloro, alkyl, hydroxy, alkoxy, cyano, amino, acetylamino, mono- or di-alkylamino, phenyl, furyl, 4-pyridyl, 1-pyrrolyl or mono- or di-C_{1-3} alkyl-1-pyrrolyl; R^3 represents hydrogen, alkyl either straight or branched chain and having from 1-5 carbon atoms, alkenyl, alkinyl, C_{3-10} cycloalkyl, preferably adamantyl, haloalkyl, preferably polyfluoroalkyl, alkoxyalkyl, hydroxyalkyl, dialkylaminoalkyl, (4-pyridyl)-C_{1-3}

alkyl, alkoxycarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, 4-alkylpiperazinylcarbonyl, piperidinocarbonyl, N-alkylthiocarbamoyl, phenyl, amidino or mono-, di- or tri-alkyl substituted amidino, 2-imidazolin-2-yl or 1-C_{1-5} alkyl substituted 2-imidazolin-2-yl, 2-, 3- or 4-pyridyl, 2-(3,4,5,6-tetrahydropyrimidinyl), 2-(3,4-dihydro-1,3-thiazolyl), and 2-(5,6-dihydro-4(H)-1,3-thiazinyl); R^2 and R^3 can be linked together to form with the pyrazole nucleus to which they are attached a 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl, a 4-C_{1-3} alkyl substituted 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl or a 6,7-dihydro-5(4H)-oxopyrazolo[1,5-a]pyrimidin-3-yl; and R^4 represents hydrogen and C_{1-3} alkyl.

In the above definitions, unless otherwise indicated, the alkyl and alkoxy groups have from 1 to 3 carbon atoms and the alkenyl and alkinyl groups have from 3 to 5 carbon atoms.

Products having the above structure wherein R^1 represents hydrogen have been found to be particularly effective agents for use in the method and formulations of this invention. Among the active agents in this subgroup of compounds those products wherein R^2 represents hydrogen, amino, acetylamino, mono- or di-alkylamino or 1-pyrrolyl and R^3 represents hydrogen, straight or branched chain alkyl, alkoxyalkyl, mono- or di-alkylcarbamoyl, 2-imidazolin-2-yl or a 1-alkyl-2-imidazolin-2-yl and R^4 is hydrogen or alkyl have been found to exhibit particularly desirable properties. The most active products for use in the method and formulations of this invention are

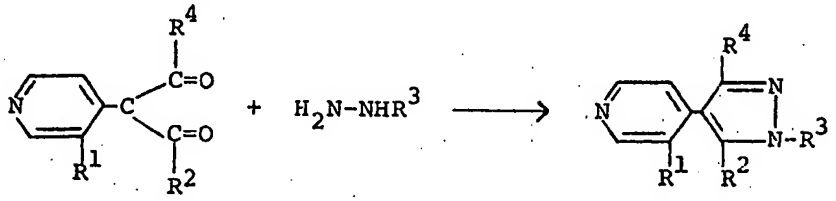
1. Products having structural formula I wherein R^1, R^2 and R^4 each represent hydrogen, and R^3 is 2-imidazolin-2-yl or a 1-alkyl-2-imidazolin-2-yl, particularly 1-methyl(or ethyl)-2-imidazolin-2-yl,

2. Products having structural formula I wherein R^1 and R^4 each represent hydrogen, R^3 is alkyl, preferably methyl and R^2 is 1-pyrrolyl or mono- or di-alkyl-1-pyrrolyl, acetylamino, di-alkylamino preferably dimethylamino or alkylamino preferably ethylamino, and

3. Products having structural formula I wherein R^1, R^2 and R^4 each represents hydrogen and R^3 is alkyl, alkoxyalkyl, dialkylcarbamoyl preferably dimethylcarbamoyl, or amidino.

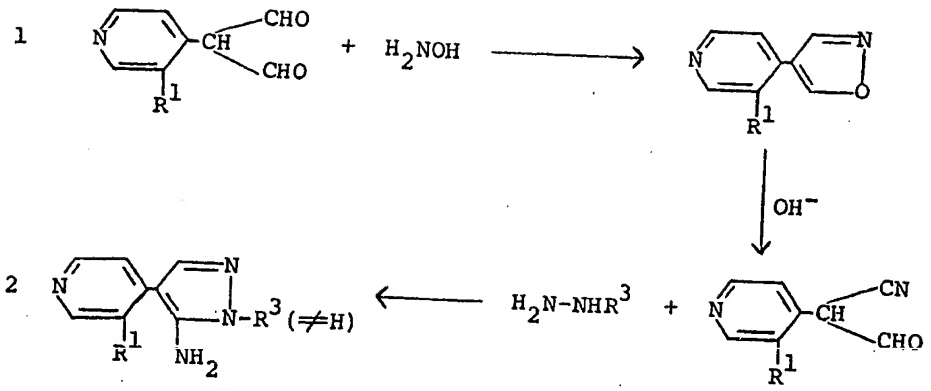
While known methods can be employed to prepare the 4-(4-pyridyl)pyrazole bronchodilating agents, the following procedures were found to be particularly suitable for making the various products employed in the method and formulation of this invention.

Most of the 4-(4-pyridyl)pyrazole products were prepared by condensing a β-dicarbonyl compound with a hydrazine derivative as schematically depicted below:



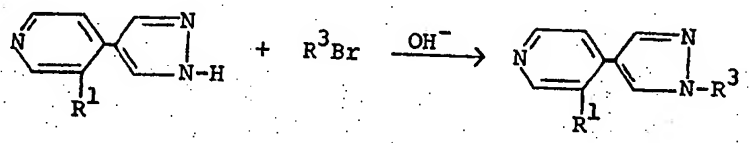
The above process conveniently is carried out at between ambient to about 100° C. in one of the following solvents: ethanol (usually with a drop of acetic acid as catalyst), dilute hydrochloric acid, 85% phosphoric acid or by an azeotropic procedure (benzene containing slightly more than 2 equivalents of acetic acid).

4-(4-Pyridyl)-5-aminopyrazoles having a substituent in the 1-position are conveniently made by the following reaction:



The first step is carried out by the reaction of the pyridine malondialdehyde and hydroxylamine preferably with moderate heating to give the 4-(4-pyridyl)isoxazole which, upon treatment with base, provides 2-formyl-2-(4-pyridyl)acetonitrile. The intermediate acetonitrile product then is reacted with the selected hydrazine in the presence of benzene and acetic acid at reflux temperature yielding the 1-substituted-4-(4-pyridyl)pyrazole.

Alternatively, the 4-(4-pyridyl)pyrazole can be alkylated in the 1-position by employing known alkylating procedures and agents as indicated by the following reaction scheme:



This alkylation conveniently is carried out at room temperature in the presence of a base, suitably sodium ethoxide. Should a substituent be present in the 3(5)-position, alkylation may give two products.

Substituents on the pyridyl ring or the pyrazole ring can be modified by known methods. For example, a nitro can be reduced to an amino, the amino converted to a cyano, acetylamino, mono- or di-alkylamino, or an amino substituent

can be replaced by chloro or hydroxy and the hydroxy converted to an alkoxy substituent or an ester group converted to an amide, all of these conversions being effected by known procedures.

Suitable pharmacologically acceptable salts of product I prepared by conventional methods are acid addition salts derived from inorganic acids for example hydrochlorides, hydrobromides, phosphates, or sulfates or salts derived from organic acids, for example, fumarates, oxalates, lactates, malates, maleates, isethionates, formates, acetates, succinates, tartrates, salicylates, citrates, phenylacetates, benzoates, p-toluenesulfonates, pamoates and other salts such as those that provide relatively insoluble products that afford a slow release of the active material, for example, a 1,1'-methylene-bis(2-hydroxy-3-naphthoate) and the like.

The 4-(4-pyridyl)pyrazoles can be administered in the method of this invention in formulations suitable for oral or parenteral administration or in aerosol preparations. Intravenous or intraduodenal doses in the range of between about 2 mg./kg. to about 75 mg./kg. provided protection at the ED_{50} level against the induced bronchoconstriction in most animals challenged. Those products that also exhibited hypotensive properties were effective within the same dosage range.

The 4-(4-pyridyl)pyrazoles can be formulated by conventional means with pharmaceutical carriers and may, if desired, be combined with other desired pharmacologically active compounds. Capsules, tablets, or liquid preparations can be prepared for oral administration, solutions or suspensions of the active ingredient can be prepared for

parenteral administration and aerosols containing the active ingredient can be prepared by conventional methods for topical application or application to mucous membranes. For example, a capsule can be prepared by conventional methods employing lactose as an excipient and containing per unit dosage 5-25 mg. of active compound, although unit dosages can range between about 5-100 mg. for administration as prescribed by the physician.

The following examples describe the preparation of certain representative 4-(4-pyridyl)pyrazole compounds that have been found to be effective bronchodilating agents in the method and formulations of this invention.

EXAMPLE 1

1-Methyl-4-(4-pyridyl)-pyrazole

A mixture of 4-pyridylmalondialdehyde (10 mmole), methylhydrazine (10.3 mmole) and 85% phosphoric acid (25 ml.) is heated on a steam bath for 5 hours. The reaction mixture then is poured into ice water and made basic with ammonium hydroxide to precipitate the crude product (44% yield). After isolation by extraction with ethyl acetate and recrystallization from petroleum ether there is obtained purified 1-methyl-4-(4-pyridyl)-pyrazole, m.p. 76-78° C.

Analysis calculated for $C_9H_9N_3$:

C, 67.90; H, 5.70; N, 26.40;

Found: C, 67.86; H, 5.64; N, 26.29.

EXAMPLE 2

1-t-Butyl-4-(4-pyridyl)-pyrazole hydrochloride

A mixture of 4-pyridylmalondialdehyde (1.49 g., 10 mmole), t-butylhydrazine hydrochloride (1.62 g., 13 mmole), sodium acetate trihydrate (1.8 g.), acetic acid (1.3 ml.) and benzene (40 ml.) is heated under reflux under a Dean Stark trap for 4 hours by which time 1.1 ml. of water is collected.

The reaction mixture is evaporated under reduced pressure and the residue is made basic with 5N sodium hydroxide solution, extracted with ethyl acetate and dried over magnesium sulfate. The dried extract is evaporated to afford 2.1 g. of free base, which is taken up in a small volume of isopropanol and acidified with ethanolic hydrogen chloride to yield 1.9 g., (80%), of 1-t-butyl-4-(4-pyridyl)-pyrazole hydrochloride, m.p. 214-216° C. Recrystallization of the salt from a mixture of isopropanol and ether raises its melting point to 215-216° C.

Analysis calculated for $C_{12}H_{15}N_3 \cdot HCl$:

C, 60.63; H, 6.78; Cl, 14.91; N, 17.68;

Found: C, 60.82; H, 7.31; Cl, 14.89; N, 17.37.

EXAMPLE 3

1-Isobutyl-4-(4-pyridyl)-pyrazole hydrogen maleate

By replacing t-butylhydrazine hydrochloride with isobutylhydrazine hydrochloride in Example 2, there is obtained 1-isobutyl-4-(4-pyridyl)-pyrazole. After the reaction mixture residue is made basic, the crude base is isolated by extraction with ethyl acetate, and then dissolved in isopropanol. One equivalent of maleic acid is added to the hot solution and on cooling, the maleate salt of the product crystallizes out in 63% yield, m.p. 137-139° C. Upon further purification by recrystallization from the same solvent the salt melts at 137-138° C.

Analysis calculated for $C_{12}H_{15}N_3 \cdot C_4H_4O_4$:

C, 60.56; H, 6.03; N, 13.24;

Found: C, 60.47; H, 5.86; N, 13.47.

EXAMPLE 4

1-Allyl-4-(4-pyridyl)-pyrazole hydrochloride

To a solution of sodium (322 mg., 14 mmole) in

ethanol (25 ml.) is added 4-(4-pyridyl)-pyrazole (2.03 g., 14 mmole), followed by allyl bromide (1.7 g., 14 mmole). The mixture is stirred at room temperature for 2 days and evaporated to dryness. The residue is leached with ether, and to the ethereal solution is added ethanolic hydrogen chloride. The precipitated solid is recrystallized from a mixture of isopropanol and ether to afford 1-allyl-4-(4-pyridyl)-pyrazole hydrochloride (1.1 g., 32%), m.p. 208-210° C. Further recrystallization of the solid raises its melting point to 210-211° C.

Analysis calculated for $C_{11}H_{11}N_3 \cdot HCl$:

C, 59.60; H, 5.45; Cl, 15.99; N, 18.95;

Found: C, 59.77; H, 5.60; Cl, 16.27; N, 19.07.

EXAMPLE 5

1-(1-Adamantyl)-4-(4-pyridyl)-pyrazole hydrochloride monohydrate

By replacing the t-butylhydrazine hydrochloride with 1-adamantylhydrazine hydrochloride in Example 2, there is obtained 1-(1-adamantyl)-4-(4-pyridyl)-pyrazole hydrochloride monohydrate in 44% yield, m.p. 315-320° C.

Analysis calculated for $C_{18}H_{21}N_3 \cdot HCl \cdot H_2O$:

C, 64.75; H, 7.24; Cl, 10.62; N, 12.59;

Found: C, 64.89; H, 7.40; Cl, 10.73; N, 12.49.

EXAMPLE 6

1-Methyl-4-(4-pyridyl)-5-amino-pyrazole hydrochloride

Step A: Preparation of 2-Formyl-2-(4-pyridyl)-acetonitrile

4-Pyridine malondialdehyde (29.8 g., 0.2 mole) is added to a solution of hydroxylamine hydrochloride (16.0 g., 0.23 mole) in water (500 ml.) and the mixture is heated at 65-70° C. for 2 hours. When cool, the solution is made basic with 10% sodium carbonate solution, the crude 4-(4-

pyridyl)-isoxazole is filtered off, washed with water and drained on the filter. The solid is suspended in water (500 ml.) and the suspension made basic with 5N sodium hydroxide (50 ml.). The suspension is heated briefly until solution occurs, then it is cooled to room temperature and acidified with acetic acid. The crude product is collected, washed with water and dried, yielding 25.4 g.(86%) of product as a pale pinkish powder. Following purification by dissolution in dilute sodium hydroxide, treatment of the solution with charcoal, and then slow acidification of the filtrate with acetic acid, a crystalline solid is obtained which decomposes above 320° C.

Analysis calculated for $C_8H_6N_2O$:

C, 65.74; H, 4.14; N, 19.17;

Found: C, 66.14; H, 4.35; N, 19.04.

Step B: Preparation of 1-Methyl-4-(4-pyridyl)-5-amino-pyrazole hydrochloride

2-Formyl-2-(4-pyridyl)-acetonitrile (10.5 g., 72 mmole) is suspended in a mixture of benzene (96 ml.) and acetic acid (9.0 ml.), and to the suspension is added methylhydrazine (4.33 g., 93.5 mmole). The reaction mixture is heated under reflux for 4-1/2 hours and water formed in the reaction is collected in a Dean-Stark trap. After standing at ambient temperature overnight, the crystalline solid is collected, dissolved in ethanol and the hydrochloride salt is formed by adding a slight excess of ethanolic hydrogen chloride solution. The product (6.3 g.) is purified by recrystallization from ethanol and then has a melting point of 295-300° C.

Analysis calculated for $C_9H_{10}N_4 \cdot HCl$:

C, 51.31; H, 5.26; N, 26.60; Cl, 16.83;

Found: C, 50.97; H, 5.10; N, 26.81; Cl, 17.10.

EXAMPLE 7

3(5)-Amino-4-(4-pyridyl)-pyrazole hydrochloride

By replacing methylhydrazine employed in Example 6, Step B, with 85% hydrazine hydrate there is obtained 3(5)-amino-4-(4-pyridyl)-pyrazole hydrochloride in 28% yield, m.p. 290-293° C. after recrystallization from a mixture of methanol and ethanol.

Analysis calculated for $C_8H_8N_4 \cdot HCl$:

C, 48.86; H, 4.61; Cl, 18.03; N, 28.49;

Found: C, 48.65; H, 4.73; Cl, 17.92; N, 28.40.

EXAMPLE 8

1-Methyl-4-(4-pyridyl)-5-chloro-pyrazole hydrochloride

To a solution of 1-methyl-4-(4-pyridyl)-5-aminopyrazole hydrochloride, prepared as described in Example 6, (421 mg., 2 mmole) in 5N hydrochloric acid (2 ml.) cooled in an ice bath, there is added finely powdered sodium nitrite (138 mg., 2 mmole) in small portions with stirring. The solution is stirred at 0-5° C. for 30 minutes to provide the diazonium salt. Meanwhile a hot (50-60° C.) solution of cupric sulfate pentahydrate (398 mg., 2 mmole) and sodium chloride (238 mg., 4 mmole) in water (1.3 ml.) is saturated with sulfur dioxide and cooled. The cuprous chloride is filtered off, washed with a little cold water and then dissolved in 5N hydrochloric acid (0.7 ml.) on a steam bath. The cuprous chloride solution is removed from the steam bath and the diazonium solution is added slowly with stirring. After stirring the mixture on a steam bath for 10 minutes, it is allowed to cool to ambient temperature, then made basic with ammonium hydroxide and the crude product isolated by extraction with ether (3 x 7 ml.). The oily crude product is dissolved in isopropanol (2 ml.), and a

slight excess of ethanolic hydrogen chloride is added to form 236 mg. of the hydrochloride, m.p. 275-278° C. (dec.). The pure product separates from alcohol in pale yellow crystals, m.p. 276.5-278.5° C. (dec.).

Analysis calculated for $C_9H_8ClN_3 \cdot HCl$:

C, 46.98; H, 3.94; Cl, 30.82; N, 18.26;

Found: C, 46.69; H, 4.05; Cl, 30.58; N, 18.09.

EXAMPLE 9

1-Methyl-4-(4-pyridyl)-5-hydroxy-pyrazole hydrochloride

1-Methyl-4-(4-pyridyl)-5-amino-pyrazole (348 mg., 2 mmole), prepared as described in Example 6, is added to trifluoroacetic acid (2 ml.), and to the stirred mixture cooled in an ice bath is added finely powdered sodium nitrite (150 mg., 2.17 mmole) in small portions over 15 minutes. The mixture is stirred in the ice bath for 15 minutes, and then at ambient temperature for 15 minutes before it is poured slowly into boiling 10% sulfuric acid (7 ml.). The solution is boiled for 15 minutes, and then cooled to ambient temperature. After partial neutralization with 10N sodium hydroxide solution (with cooling), basification of the reaction mixture is completed with solid sodium carbonate. The crude product (197 mg.), is isolated by continuous extraction with methylene chloride for 24 hours, and purified by chromatography on silica gel using ethyl acetate as the solvent. The product is contained in the first fraction to be eluted: the free base is dissolved in isopropanol (1 ml.), and a slight excess of ethanolic hydrogen chloride is added to precipitate the hydrochloride salt. The solid (100 mg.) is recrystallized from a mixture of ethanol and isopropanol affording 61 mg. of product as slightly hygroscopic crystals, m.p. 185-195° C. (dec.).

Analysis calculated for $C_9H_9N_3O \cdot HCl$:

C, 51.07; H, 4.76; Cl, 16.75; N, 19.85;

Found: C, 50.47; H, 5.58; Cl, 16.40; N, 19.96.

EXAMPLE 10

1-Methyl-4-(4-pyridyl)-5-cyano-pyrazole hydrochloride

1-Methyl-4-(4-pyridyl)-5-amino-pyrazole (348 mg., 2 mmole), prepared as described in Example 6, in trifluoroacetic acid (2 ml.) at 0-5° C. is diazotized by the addition, in small portions, of finely powdered sodium nitrite (150 mg., 2.17 mmole). After stirring the mixture for one hour at ambient temperature, the solution is diluted with water (4 ml.) and partially neutralized with sodium carbonate (0.5 g.) added in small portions with stirring. This solution then is added slowly to a solution of cuprous cyanide (896 mg., 10 mmole) and sodium cyanide (1.416 g., 24 mmole) in water (6 ml.) at 40° C. The reaction mixture is kept at 40° C. for 15 minutes, and then adjusted to ca. pH 10 with ammonium hydroxide. The crude free base is isolated by ether extraction and converted to a hydrochloride salt by addition of an ethanolic hydrogen chloride solution, yielding 55 mg. (12-1/2%) of product, m.p. 255-260° C. Following further purification by recrystallization from alcohol, the product melts at 261-263° C. as slightly hygroscopic crystals.

Analysis calculated for $C_{10}H_8N_4 \cdot HCl$:

C, 54.43; H, 4.11; Cl, 16.07; N, 25.39;

Found: C, 53.90; H, 4.53; Cl, 16.25; N, 25.11.

EXAMPLE 11

1-Methyl-4-(4-pyridyl)-5-acetamido-pyrazole hydrochloride

A mixture of 1-methyl-4-(4-pyridyl)-5-amino-pyrazole (1.0 g., 5.75 mmole), prepared as described in Example 6, and acetic anhydride (5 ml.) is heated on a steam bath

for 3 hours and then evaporated under vacuum. The residue is dissolved in isopropanol and ethanolic hydrogen chloride is added. Precipitation of the product is completed by adding dry ether and following recrystallization from ethanol, there is obtained 520 mg. (36%) of product, m.p. 298-301° C.

Analysis calculated for $C_{11}H_{12}N_4O \cdot HCl$:

C, 52.28; H, 5.18; Cl, 14.03; N, 22.17;

Found: C, 51.97; H, 5.17; Cl, 13.88; N, 22.24.

EXAMPLE 12

1-Methyl-4-(4-pyridyl)-5-dimethylamino-pyrazole

A mixture of 1-methyl-4-(4-pyridyl)-5-amino-pyrazole (2.98 g., 20 mmole), prepared as described in Example 6, 88% formic acid (5 ml.) and 40% formaldehyde (10 ml.) is heated under reflux in an oil bath at 120-130° C. for 40 hours, and then evaporated under reduced pressure. The residue is dissolved in a little water, the solution made basic with ammonium hydroxide and the product extracted with ethyl acetate. Evaporation of the ethyl acetate affords crude product which, on recrystallization from water, gives 1.65 g. (41%) of purified product in the form of colorless needles, m.p. 121.5-123° C.

Analysis calculated for $C_{11}H_{14}N_4$:

C, 65.32; H, 6.98; N, 27.70;

Found: C, 65.33; H, 7.00; N, 28.21.

EXAMPLE 13

1-t-Butyl-4-(4-pyridyl)-5-amino-pyrazole hydrochloride monohydrate

By replacing methylhydrazine employed in Example 6 with an equivalent quantity of t-butylhydrazine hydrochloride plus an equivalent amount of sodium acetate, there is obtained 1-t-butyl-4-(4-pyridyl)-5-amino-pyrazole. The

free base is isolated by evaporating the reaction mixture to dryness, dissolving the residual oil in water, adding ammonium hydroxide and extracting with ethyl acetate. The crude base obtained by evaporation of the extract is dissolved in isopropanol and a slight excess of ethanolic hydrogen chloride is added. The solid is collected and recrystallized from a mixture of isopropanol and ether containing charcoal giving product, m.p. 230° C. The crystals are hydrated.

Analysis calculated for $C_{12}H_{16}N_4 \cdot HCl \cdot H_2O$:

C, 53.23; H, 7.07; Cl, 13.09; N, 20.69;

Found: C, 53.15; H, 7.56; Cl, 13.27; N, 20.41.

EXAMPLE 14

1-Methyl-4-(3-nitro-4-pyridyl)-pyrazole

Step A: Preparation of (3-Nitro-4-pyridyl)malondialdehyde

To dimethylformamide (22 g., 0.3 mole) is added with stirring and cooling phosphorus oxychloride (9.2 g., 0.06 mole). After 15 minutes, 3-nitro-4-picoline hydrochloride (3.5 g., 0.02 mole) is added. The reaction mixture then is heated at 70° C. for 6 hours and left at room temperature overnight. The reaction mixture is poured onto 70 g. of ice and brought to alkaline pH with concentrated ammonium hydroxide. After stirring for 10 minutes, the reaction mixture is heated on the steam bath for another 10 minutes, cooled with an ice bath and the pH adjusted to 4 with concentrated hydrochloric acid. The volume is reduced on the flash evaporator to half the original volume and left in the refrigerator for several hours. The salt is filtered off, washed with a small amount of water and the filtrate evaporated to half its volume and left in the refrigerator overnight. The crystals are filtered, washed with ice cold methanol and air dried yielding 0.85 g. of product, m.p. 178° C.

Analysis calculated for $C_8H_6N_2O_4 \cdot H_2O$:

N, 13.20;

Found: N, 13.15.

Step B: Preparation of 1-methyl-4-(3-nitro-4-pyridyl)-pyrazole

The (3-nitro-4-pyridyl)malondialdehyde (5 g., 26 mmoles) and methylhydrazine (1.2 g.) are reacted in 25 ml. 2N hydrochloric acid. Heating on the steam bath is continued for two hours, the reaction mixture then is made basic with sodium hydroxide and extracted with ether. The ethereal phase is dried over magnesium sulfate and taken to dryness, the residue dissolved in boiling petroleum ether, the insolubles decanted and the petroleum fraction taken to dryness yielding 1 g. of 1-methyl-4-(3-nitro-4-pyridyl)-pyrazole, m.p. 68-70° C.

Analysis calculated for $C_9H_8N_4O_2$:

C, 52.94; H, 3.95; N, 27.44;

Found: C, 52.57; H, 3.84; N, 27.12.

EXAMPLE 15

1-Methyl-4-(3-amino-4-pyridyl)-pyrazole

1-Methyl-4-(3-nitro-4-pyridyl)-pyrazole, (Example 14) (3 g., 14.5 mmoles) is dissolved in concentrated hydrochloric acid (12 ml.). Hydrated stannous chloride (21 g., 0.1 mole) in 12 ml. concentrated hydrochloric acid is added and the reaction progresses readily. The solid material is separated by filtration and dried yielding 1-methyl-4-(3-amino-4-pyridyl)-pyrazole, m.p. 134-137° C.

Analysis calculated for $C_9H_{10}N_4$:
C, 62.05; H, 5.79; N, 32.16;
Found: C, 62.14; H, 5.95; N, 31.86.

EXAMPLE 16

1-Methyl-4-(3-acetamido-4-pyridyl)-pyrazole hydrogen maleate

1-Methyl-4-(3-amino-4-pyridyl)-pyrazole (Example 15) (100 mg., 0.5 mmole) is added to 10 ml. pyridine and 5 ml. acetic anhydride. The solution is heated on the steam bath overnight, the reaction mixture then flashed down to dryness and the resulting oil dissolved in 5 ml. isopropanol. Maleic acid (116 mg., 1 mmole) in 5 ml. isopropanol is added and the solution slowly concentrated until there is an indication of crystallization. The solution is placed in the refrigerator for several hours, the solid maleate salt is filtered off, washed with cold isopropanol and air dried, yielding 90 mg. of 1-methyl-4-(3-acetamido-4-pyridyl)-pyrazole hydrogen maleate, m.p. 125-126° C.

NMR: ppm: 8.97 s(1H, pyrazole proton); 8.68 s(1H, pyrazole proton); 6.35 s(2H, maleate protons); 3.99 s(3H, $N-CH_3$); 2.15 s(3H, $COCH_3$).

Note: The NMR's reported for some of the compounds were run in DMSO except where otherwise noted.

EXAMPLE 17

1-Methyl-4-(3-dimethylamino-4-pyridyl)-pyrazole hydrogen maleate monohydrate

1-Methyl-4-(3-amino-4-pyridyl)-pyrazole (Example 15) (100 mg., 0.5 mmole) is added to 1 ml. of formaldehyde (37% v/v) and 2 ml. formic acid. The materials are refluxed on the steam bath overnight when analysis by TLC (thin layer chromatography) will show the reaction is complete. The resulting solution is made basic with sodium hydroxide and extracted with ethyl acetate. The oily residue, obtained after evaporation of the solvent, is treated with 87 mg. maleic acid in 5 ml. isopropanol. As no precipitate is formed, the isopropanol solution is evaporated to dryness and the oil slowly crystallizes yielding 120 mg. of 1-methyl-4-(3-dimethylamino-4-pyridyl)-pyrazole hydrogen maleate monohydrate, m.p. 139° C.

Analysis calculated for $C_{11}H_{14}N_4 \cdot C_4H_4O_4 \cdot H_2O$:

C, 53.56; N, 5.99;

Found: C, 53.47; N, 5.60.

EXAMPLE 18

1-Methyl-4-(3-phenyl-4-pyridyl)-pyrazole

1-Methyl-4-(3-amino-4-pyridyl)-pyrazole (Example 15) (150 mg., 0.73 mmole) is treated with isoamyl nitrite (0.5 ml.) in 10 ml. benzene and the solution refluxed for 2 hours. The reaction mixture is pumped to dryness, water is added and the mixture then made basic with sodium hydroxide and extracted with ethyl acetate. A TLC analysis shows the residue contains two components which are separated by preparative TLC. The 1-methyl-4-(3-phenyl-4-pyridyl)-pyrazole is obtained as an oil, yield 52 mg. The second component is 1-methyl-4-(4-pyridyl)-pyrazole.

NMR: ppm: 7.40 s(5H, phenyl proton); 7.35 s(1H, pyrazole proton); 6.99 s(1H, pyrazole proton); 3.77 s(3H, N-CH_3).

Mass Spectrum: M^+ 235.

EXAMPLE 19

1-Methyl-4-(3-hydroxy-4-pyridyl)-pyrazole

1-Methyl-4-(3-amino-4-pyridyl)-pyrazole (Example 15) (150 mg., 0.73 mmole) is dissolved in 5 ml. of water containing 250 mg. concentrated sulfuric acid and the solution stirred in an ice bath while sodium nitrite (83 mg.) in 1 ml. of ice cold water is added dropwise. The resulting solution containing the diazonium salt is stirred in the ice bath for an additional hour. Water (3.2 ml.) and concentrated sulfuric acid (0.8 ml.) are placed in a separate 50 ml. flask. The solution is warmed on the steam bath and the diazonium salt solution added with a pipet. After heating for 5 minutes, TLC shows that the reaction is complete. The reaction mixture is adjusted to pH 7 and the solution placed in the refrigerator overnight. The crystals are filtered and air dried yielding 1-methyl-4-(3-hydroxy-4-pyridyl)-pyrazole, (90 mg.), m.p. 164-165° C.

NMR: ppm: 8.34 s(1H, pyrazole proton); 8.21 s(1H, pyrazole proton); 3.98 s(3H, N-CH_3).

Mass Spectrum: M^+ 175.

EXAMPLE 20

1-Methyl-4-(3-Chloro-4-pyridyl)-pyrazole hydrogen maleate hemihydrate

1-Methyl-4-(3-amino-4-pyridyl)-pyrazole (Example 15) (125 mg., 0.71 mmole) is dissolved in 6 ml. of water and 4 ml. of 1N hydrochloric acid. The solution is stirred and kept cooled in an ice bath as 80 mg. sodium nitrite dissolved in 1 ml. water is added. The reaction is stirred

in the cold for one hour. The diazonium salt is pipetted onto cuprous chloride (200 mg.) in concentrated hydrochloric acid (2 ml.) while maintaining the temperature at about 75° C. The resulting mixture is heated on the steam bath for an hour, the solution then made basic, the copper hydroxide filtered off and the solution extracted with ethyl acetate. The ethyl acetate extract is concentrated under vacuum and the product pumped dry under high vacuum. The maleate salt is prepared in the usual manner (Example 16) yielding 250 mg. of 1-methyl-4-(3-chloro-4-pyridyl)-pyrazole hydrogen maleate hemihydrate, m.p. 139-141° C.

Analysis calculated for $C_9H_8ClN_3 \cdot C_4H_4O_4 \cdot 1/2\ H_2O$:
C, 48.99; H, 4.11; N, 13.18; Cl, 11.12;
Found: C, 49.06; H, 4.29; N, 12.68; Cl, 10.87.

EXAMPLE 21

1-Methyl-4-(3-cyano-4-pyridyl)-pyrazole hemihydrate

1-Methyl-4-(3-amino-4-pyridyl)-pyrazole (Example 15) (154 mg., 1 mmole) is dissolved in 5 ml. of 1N hydrochloric acid and the solution stirred in an ice bath as 80 mg. of sodium nitrite dissolved in 1 ml. water is added dropwise. The diazonium solution is then stirred in the cold for an additional hour. The solution is neutralized with sodium carbonate and the neutral diazonium salt added to a hot solution of potassium cuprous cyanide prepared by dissolving cuprous cyanide in potassium cyanide. The reaction mixture then is heated one hour on the steam bath, cooled and extracted with ethyl acetate. After drying over magnesium sulfate and removing the solvent under vacuum, there is obtained 150 mg. of 1-methyl-4-(3-cyano-4-pyridyl)-pyrazole hemihydrate, m.p. 148-151° C.

Analysis calculated for $C_{10}H_8N_4 \cdot 1/2\ H_2O$:

C, 62.16; H, 4.69; N, 29.00;

Found: C, 61.79; H, 4.63; N, 28.71.

EXAMPLE 22

1-(2,2,2-Trifluoroethyl)-4-(4-pyridyl)-pyrazole

A mixture of 4-pyridylmalondialdehyde (3.53 g., 23.6 mmole), 70% 2,2,2-trifluoroethylhydrazine (3.86 g., 23.6 mmole) and alcohol (50 ml.) is heated under reflux for 3 hours, and then evaporated to dryness. The residual solid is recrystallized from di-isopropyl ether to afford 2.75 g. (60%) of product, m.p. 109-111° C.

Analysis calculated for $C_{10}H_8F_3N_3$:

C, 52.87; H, 3.55; F, 25.09; N, 18.49;

Found: C, 52.95; H, 3.56; F, 25.31; N, 18.40.

EXAMPLE 23

1-(2-Hydroxyethyl)-4-(4-pyridyl)-pyrazole

A mixture of 4-pyridylmalondialdehyde (2.98 g., 20 mmole), 2-hydroxyethylhydrazine (1.52 g., 20 mmole) and 1N hydrochloric acid (40 ml.) is heated briefly until complete solution is obtained, and then allowed to stand at room temperature for 2 hours. After the reaction is made basic with ammonium hydroxide, the product is isolated by continuous extraction with methylene chloride and purified by recrystallization from benzene yielding 1.1 g. (29%) of product, m.p. 114-116° C.

Analysis calculated for $C_{10}H_{11}N_3O$:

C, 63.48; H, 5.86; N, 22.21;

Found: C, 63.58; H, 5.94; N, 22.31.

EXAMPLE 24

1-(2-Methoxyethyl)-4-(4-pyridyl)-pyrazole hydrochloride

A mixture of 4-pyridylmalondialdehyde (7.5 g., 50

mmole), methoxyethylhydrazine (5.85 g., 65 mmole), acetic acid (6.5 ml.) and benzene (200 ml.) is stirred at reflux under a Dean-Stark trap for 4-1/2 hours and then evaporated in a rotary evaporator. The residual oil is treated with dry ether and a slight excess of ethanolic hydrogen chloride is added to precipitate the hydrochloride of the product. This somewhat hygroscopic solid is dissolved in isopropanol and carefully reprecipitated by adding dry ether. The salt is dried and stored over calcium chloride in a vacuum desiccator, yielding 7.3 g. (61%) of product, m.p. 127-129° C.

Analysis calculated for $C_{11}H_{13}N_3O \cdot HCl$:

C, 55.12; H, 5.88; N, 17.53; Cl, 14.79;

Found: C, 54.41; H, 6.17; N, 17.58; Cl, 14.96.

EXAMPLE 25

1-(2-Dimethylaminoethyl)-4-(4-pyridyl)-pyrazole dihydrochloride

A mixture of 4-pyridylmalondialdehyde (1.49 g., 10 mmole), 2-dimethylaminoethylhydrazine (1.34 g., 13 mmole), acetic acid (1.5 ml.) and benzene (40 ml.) is heated at reflux under a Dean-Stark trap overnight. The solvent is evaporated under vacuum and the oily residue is made basic with 10N sodium hydroxide (3 ml.) and partitioned between ethyl acetate and water. The ethyl acetate extract is dried over magnesium sulfate and evaporated to afford a pale yellow oil. Dissolution of the oil in isopropanol and acidification with hydrogen chloride in ethanol gives 2 g. of the hydrochloride of the product as a hygroscopic solid which, after recrystallization from absolute ethanol affords 1.25 g. of pure material, m.p. 253-255° C.

Analysis calculated for $C_{12}H_{16}N_4 \cdot 2HCl$:

C, 49.83; H, 6.27; Cl, 24.52; N, 19.37;

Found: C, 49.95; H, 6.40; Cl, 24.29; N, 19.22.

The di(hydrogen maleate)salt of 1-(2-dimethylaminoethyl)-4-(4-pyridyl)-pyrazole is prepared by the process described in Example 16, employing an excess of maleic acid, giving product melting at 137-138° C. (dec.).

Analysis calculated for $C_{12}H_{16}N_4 \cdot 2C_4H_4O_4$:

C, 53.57; H, 5.39; N, 12.49;

Found: C, 53.65; H, 5.45; N, 12.32.

EXAMPLE 26

1-(4-Pyridylmethyl)-4-(4-pyridyl)-pyrazole

A mixture of 4-picolylhydrazine dihydrochloride (1.75 g., 8.92 mmole), 4-pyridylmalondialdehyde (1.33 g., 8.92 mmole) and water (20 ml.) is heated for a few minutes on a steam bath until the aldehyde dissolves, and the solution is allowed to stand at ambient temperature for 2 hours, before being made basic with ammonium hydroxide. The solid is collected, washed with water and dried to provide 1.35 g. (64%) of product, m.p. 129-134° C. Further recrystallization from di-isopropyl ether raises the melting point to 133-135° C.

Analysis calculated for $C_{14}H_{12}N_4$:

C, 71.17; H, 5.12; N, 23.71;

Found: C, 71.35; H, 5.11; N, 23.83.

EXAMPLE 27

1-[2-(4-Pyridyl)-ethyl]-4-(4-pyridyl)-pyrazole dihydrochloride dihydrate

A mixture of 4-pyridylmalondialdehyde (5.96 g., 40 mmole), 4-(2-hydrazinoethyl)-pyridine (7.1 g., 52 mmole), acetic acid (5.2 ml.) and benzene (160 ml.) is stirred at

reflux under a Dean-Stark trap for 4-1/2 hours. The reaction mixture is evaporated and the residue is dissolved in isopropanol. Addition of a slight excess (>2 equivalents) of ethanolic hydrogen chloride yields the crude hydrochloride as a precipitate. The solid is collected and recrystallized from ethanol to afford 6.2 g. (45%) of product, m.p. 252-254° C.

Analysis calculated for $C_{15}H_{14}N_4 \cdot 2HCl \cdot 2H_2O$:

C, 50.15; H, 5.60; Cl, 19.73; N, 15.59;

Found: C, 50.05; H, 6.29; Cl, 19.52; N, 15.53.

EXAMPLE 28

Ethyl [4-(4-pyridyl)-1-pyrazolyl]-acetate

By replacing t-butylhydrazine hydrochloride in Example 2 by an equivalent quantity of ethyl hydrazinoacetate hydrochloride and following substantially the same procedure, there is obtained ethyl [4-(4-pyridyl)-1-pyrazolyl]-acetate in 88% yield. The compound crystallizes from water in colorless plates, m.p. 96.5-97.5° C.

Analysis calculated for $C_{12}H_{13}N_3O_2$:

C, 62.32; H, 5.66; N, 18.17;

Found: C, 61.98; H, 5.84; N, 17.81.

EXAMPLE 29

[4-(4-Pyridyl)-1-pyrazolyl]-N,N-dimethyl acetamide hydrochloride

Ethyl [4-(4-pyridyl)-1-pyrazolyl]-acetate (Example 28) (2.31 g., 10 mmoles) is dissolved in ethanol (10 ml.) saturated with dimethylamine and left at ambient temperature for three days. The solvent then is removed under vacuum, leaving an oil that slowly crystallizes. The yield is essentially quantitative, with a recovery of 2.25 g. of [4-(4-pyridyl)-1-pyrazolyl]-N,N-dimethyl acetamide hydrochloride, m.p. 286-288° C.

Analysis calculated for $C_{12}H_{14}N_4O \cdot HCl$:

C, 54.03; H, 5.67; N, 21.01; Cl, 13.29;

Found: C, 54.40; H, 6.36; N, 20.87; Cl, 13.26.

EXAMPLE 30

1-Ethylcarbamoyl-4-(4-pyridyl)-pyrazole

A mixture of 4-(4-pyridyl)-pyrazole (600 mg., 4 mmole), ethyl isocyanate (10 ml.) and triethylamine (1 ml.) is heated under reflux for 3 hours and then evaporated to dryness. The residue is recrystallized from ethyl acetate to give 400 mg., (46%) of product, m.p. 159-163° C.

Analysis calculated for $C_{11}H_{12}N_4O$:

C, 61.10; H, 5.59; N, 25.91;

Found: C, 60.87; H, 5.68; N, 26.05.

EXAMPLE 31

1-Dimethylcarbamoyl-4-(4-pyridyl)-pyrazole

A mixture of 4-pyridylmalondialdehyde (3.0 g., 20 mmole), 4,4-dimethylsemicarbazide (2.06 g., 20 mmole) and 2N hydrochloric acid (20 ml.) is warmed briefly to effect solution, and then set aside at ambient temperature overnight. Addition of 2N sodium hydroxide solution (21 ml.) precipitates the crude product, 3.4 g., m.p. 123-127° C. Recrystallization of the solid from water affords 2.3 g. (54%) of 1-dimethylcarbamoyl-4-(4-pyridyl)-pyrazole, m.p. 130-131° C.

Analysis calculated for $C_{11}H_{12}N_4O$:

C, 61.10; H, 5.59; N, 25.91;

Found: C, 60.66; H, 5.89; N, 25.83.

By replacing the 4,4-dimethylsemicarbazide in Example 31 by an equivalent quantity of 4,4-di-isopropylsemicarbazide and following substantially the same procedure there is obtained 1-di-isopropylcarbamoyl-4-(4-pyridyl)-pyrazole.

EXAMPLE 32

1-(4-Methylpiperazinocarbonyl)-4-(4-pyridyl)-pyrazole

4-Pyridylmalondialdehyde (3.0 g., 20 mmole) is dissolved in 1N hydrochloric acid (40 ml.) and 4-methylpiperazine-1-carboxylic acid hydrazide (3.16 g., 20 mmole) is added. The mixture is heated briefly on a steam bath to get a clear solution and allowed to stand at room temperature for 3 hours and then neutralized with 2N sodium hydroxide (20 ml.). The solid is collected and recrystallized from hot water (ca. 60 ml.) giving 3.8 g. (69%) of product in colorless needles, m.p. 139-140° C.

Analysis calculated for $C_{14}H_{17}N_5O$:

C, 61.97; H, 6.31; N, 25.81;

Found: C, 61.71; H, 6.44; N, 26.25.

EXAMPLE 33

1-Piperidinocarbonyl-4-(4-pyridyl)-pyrazole

Replacement of 4-methylpiperazine-1-carboxylic acid hydrazide in Example 32 with an equivalent quantity of piperidine-1-carboxylic acid hydrazide and following the procedure there described, there is obtained 1-piperidinocarbonyl-4-(4-pyridyl)-pyrazine in 53% yield, m.p. 157-161° C. after recrystallization from water.

Analysis calculated for $C_{14}H_{16}N_4O$:

C, 65.60; H, 6.29; N, 21.86;

Found: C, 65.73; H, 6.51; N, 21.85.

EXAMPLE 34

1-Phenyl-4-(4-pyridyl)-pyrazole

A mixture of 4-pyridylmalondialdehyde (1.49 g., 10 mmole), phenylhydrazine hydrochloride (1.44 g., 10 mmole), 1N hydrochloric acid (10 ml.) and water (10 ml.) is heated briefly on a steam bath until solution occurs and is allowed to stand at ambient temperature for 3 hours before addition of 2N sodium hydroxide (10.5 ml.). The solid is collected, washed with water and dried yielding 1.85 g. (83%) of product, m.p. 127-130° C. On recrystallization from a mixture

of benzene and petroleum ether, the melting point is raised to 130-132° C.

Analysis calculated for $C_{14}H_{11}N_3$:

C, 76.00; H, 5.01; N, 18.99;

Found: C, 75.71; H, 5.21; N, 19.47.

EXAMPLE 35

1-Amidino-4-(4-pyridyl)-pyrazole

By replacing methylhydrazine in Example 1 with an equivalent quantity of aminoguanidine bicarbonate and following substantially the same procedure, there is obtained 1-amidino-4-(4-pyridyl)-pyrazole in 59% yield, m.p. 143-145° C. after recrystallization from water. The compound also exists in a crystalline form of m.p. 158-160° C.

Analysis calculated for $C_9H_9N_5$:

C, 57.74; H, 4.84; N, 37.41;

Found: C, 57.60; H, 4.78; N, 37.74.

The base forms a salt with isethionic acid, m.p. 173-173.5° C. following recrystallization from aqueous methanol.

Analysis calculated for $C_9H_9N_5 \cdot C_2H_6O_4S$:

C, 42.17; H, 4.83; N, 22.35; S, 10.23;

Found: C, 42.24; H, 4.73; N, 22.22; S, 10.18.

EXAMPLE 36

1-Methylamidino-4-(4-pyridyl)-pyrazole

By replacing phenylhydrazine hydrochloride in Example 34 with an equivalent quantity of 1-amino-4-methylguanidine hydriodide and following substantially the same procedure, there is obtained 1-methylamidino-4-(4-pyridyl)-pyrazole in 62% yield, m.p. 139-141° C. after recrystallization from water.

Analysis calculated for $C_{10}H_{11}N_5$:

C, 59.69; H, 5.51; N, 34.80;

Found: C, 59.38; H, 5.73; N, 35.07.

EXAMPLE 37

1-(2-Imidazolin-2-yl)-4-(4-pyridyl)-pyrazole

Step A: Preparation of 2-Hydrazino-2-imidazoline hydriodide

2-Methylthio-4,5-dihydroimidazole hydriodide (24.4 g., 0.1 mole) and hydrazine (3.2 g., 0.1 mole) are refluxed in 50 ml. absolute ethanol for a period of two hours. A strong odor of methanethiol will be detected. The reaction mixture is left at ambient temperature overnight. Ether (300 ml.) then is added to ensure complete precipitation of the product which is filtered and air dired to yield 22.2 g. (98%) of product, m.p. 123-128° C.

Step B: Preparation of 1-(2-Imidazolin-2-yl)-4-(4-pyridyl)-pyrazole·1.5 H_2O

4-Pyridylmalondialdehyde (1.5 g., 10 mmoles) and the hydrazine derivative obtained in Step A (2.3 g., 10 mmoles) are heated in 1N hydrochloric acid (10 ml.) for one hour. The resulting solution is made basic and the solid removed by filtration, washed with water and air dried yielding 1.4 g. (66%) of product, m.p. 135-138° C.

Analysis calculated for $C_{11}H_{11}N_5 \cdot 1.5\ H_2O$:

C, 54.81; H, 5.92;

Found: C, 54.99; H, 5.87.

EXAMPLE 38

4-(4-Pyridyl)-1-[2-(3,4-dihydro-1,3-thiazolyl)]-pyrazole
and
4-(4-Pyridyl)-1-[2-(5,6-dihydro-4(H)-1,3-thiazinyl)]-pyrazole

Step A-1: Preparation of 2-Hydrazino-4,5-dihydro-1,3-thiazole hydriodide

2-Methylthio-4,5-dihydro-1,3-thiazole hydriodide (6 g., 25 mmoles) and 85% hydrazine hydrate (1.5 g., 25

mmoles) are refluxed in methanol (25 ml.) for two hours, then cooled and ether (150 ml.) added. The solid is filtered and air dried giving a 52% yield of product, m.p. 148-150° C.

Analysis calculated for $C_3H_7N_3S \cdot HI$:

C, 14.70; H, 3.29; N, 17.15; S, 13.08; I, 51.78;

Found: C, 15.02; H, 3.45; N, 17.15; S, 13.66; I, 51.51.

Step A-2: Preparation of 2-Hydrazino-5,6-dihydro-4(h)-1,3-thiazine hydriodide

In a similar fashion, from 2-methylthio-5,6-dihydro-4(H)-1,3-thiazine hydriodide (6 g., 20 mmoles) and 85% hydrazine hydrate (1.2 g., 20 mmoles), 2-hydrazino-5,6-dihydro-4(H)-1,3-thiazine hydriodide is obtained in a yield of 85% (5 g.), m.p. 158-159° C.

NMR: ppm: 10.5 (1H, NH proton); 6.2 (1H, NH proton); 3.5 t(2H, CH_2 α to N, J = 7 Hz); 3.2 t(2H, CH_2 α to S, J = 7 Hz); 2.10 quintet(2H, middle CH_2, J = 7 Hz).

Step B-1: Preparation of 4-(4-Pyridyl)-1-[2-(3,4-dihydro-1,3-thiazolyl)]-pyrazole·hemihydrate

4-Pyridylmalondialdehyde (1.5 g., 10 mmoles) and the hydrazine from Step A-1 (2.5 g., 10 mmoles) are heated on the steam bath in 10 ml. of water. The heating is stopped when the malondialdehyde is completely dissolved, the reaction mixture cooled and the solution made basic by addition of sodium hydroxide. The solid is filtered and air dried to give 1.5 g. (65%) of product, m.p. 152-153° C.

Analysis calculated for $C_{11}H_{10}N_4S \cdot 1/2\ H_2O$:

C, 55.21; H, 4.63; N, 23.41;

Found: C, 55.98; H, 5.08; N, 23.57.

Step B-2: Preparation of 4-(4-Pyridyl)-1-[2-(5,6-dihydro-4(H)-1,3-thiazinyl)]-pyrazole

In a similar fashion, from the hydrazine of Step A-2, (2.5 g., 10 mmoles) and 4-pyridylmalondialdehyde (1.5 g., 10 mmoles), 4-(4-pyridyl)-1-[2-(5,6-dihydro-4(H)-1,3-thiazinyl)]-pyrazole is obtained in 70% yield, m.p. 162-163° C.

NMR: ppm: 9.18 s(1H, pyrazole proton); 8.78 d(1H, α proton, J = 6 Hz); 8.52 s(1H, pyrazole proton); 7.85 d(1H, β proton, J = 6 Hz); 3.95 and 3.20 t(2H, CH_2 α to N and S, J = 7 Hz); 1.95 q(2H, middle CH_2, J = 7 Hz).

EXAMPLE 39

3,4-Di(4-pyridyl)-pyrazole·dihydrochloride monohydrate

To 4-pyridylmethyl 4-pyridyl ketone (3.88 g., 20 mmoles) in benzene (20 ml.) is added sodium methoxide (1 g.) and ethyl formate (1.4 g.). The reaction mixture is heated at reflux for one hour and then cooled to ambient temperature. The sodium salt of the keto aldehyde formed is filtered off, washed with benzene and ether and reacted with hydrazine hydrate (1.2 g.), glacial acetic acid (1.2 g.) and water (40 ml.). The mixture is heated on the steam bath for one hour, the reaction mixture then made basic with sodium hydroxide and extracted with ethyl acetate. The solvent is dried over magnesium sulfate and concentrated under vacuum. The residue is recrystallized from chloroform-petroleum ether, yielding 1 g. of product, m.p. 128-130° C. The hydrochloride monohydrate is prepared in the usual manner, m.p. 190-192° C. (dec.).

Analysis calculated for $C_{13}H_{10}N_4 \cdot 2HCl \cdot H_2O$:
C, 49.54; H, 5.12; N, 17.77; Cl, 22.50;
Found: C, 50.03; H, 4.84; N, 17.89; Cl, 22.30.

EXAMPLE 40

1-[2-(3,4,5,6-Tetrahydropyrimidinyl)]-4-(4-pyridyl)-pyrazole trihydrochloride, hemihydrate

Step A: Preparation of 2-Hydrazino-3,4,5,6-tetrahydropyrimidine hydriodide

2-Methylmercapto-3,4,5,6-tetrahydropyrimidine hydriodide (25.8 g., .1 mole) and hydrazine (3.2 g., 0.1 mole) are refluxed in methanol (50 ml.) for two hours, (a strong odor of methanethiol is detected) and then left at ambient temperature overnight. Ether (300 ml.) is added to ensure complete precipitation of the product in the form of its hydriodide salt which is filtered and air dried yielding 22.8 g. (98%) of product, m.p. 160° C.

Analysis calculated for $C_4H_{11}N_4I$:

C, 19.85; H, 4.58; N, 23.15; I, 52.43;

Found: C, 19.95; H, 4.73; N, 23.30; I, 52.63.

Step B: Preparation of 1-[2-(3,4,5,6-Tetrahydropyrimidyl)]-4-(4-pyridyl)-pyrazole trihydrochloride hemihydrate

4-Pyridylmalondialdehyde (1.5 g., 10 mmoles) and the hydrazine derivative of Step A (2.5 g., 10 mmoles) are heated in 1N hydrochloric acid (10 ml.) for one hour. The resulting solution is made basic with ammonium hydroxide and the solid is filtered, washed with water and air dried, yielding 1.5 g. (65%) of product, m.p. 296-298° C. The hydrochloride salt is prepared by crystallizing from hydrochloric acid, m.p. 301-304° C.

Analysis calculated for $C_{12}H_{13}N_5 \cdot 3HCl \cdot 1/2\ H_2O$:

C, 41.70; H, 4.95; N, 20.26;

Found: C, 41.34; H, 4.65; N, 20.36.

EXAMPLE 41

1,4-Di-(4-pyridyl)-pyrazole

A mixture of 4-pyridylmalondialdehyde (1.49 g.,

10 mmole), 4-hydrazinopyridine hydrochloride (1.5 g., 10.3 mmole) and 85% phosphoric acid (25 ml.) is heated on a steam bath for 5 hours, then poured into ice water and made basic with ammonium hydroxide to precipitate the crude product, which on recrystallization from water (ca. 90 ml.) separates in long colorless needles, m.p. 146-147° C., 1.9 g. (86%).

Analysis calculated for $C_{13}H_{10}N_4$:

C, 70.25; H, 4.54; N, 25.21;

Found: C, 70.76; H, 4.63; N, 24.70.

EXAMPLE 42

1-(3-Pyridyl)-4-(4-pyridyl)-pyrazole

By replacing in the reaction described in Example 41 the 4-hydrazinopyridine hydrochloride with an equivalent amount of 3-hydrazinopyridine oxalate, there is obtained 1-(3-pyridyl)-4-(4-pyridyl)-pyrazole. After making the reaction mixture basic the product is isolated by extraction with ethyl acetate. Following recrystallization from benzene and treatment with charcoal there is obtained a 55% yield of product, m.p. 153-155° C.

Analysis calculated for $C_{13}H_{10}N_4$:

C, 70.25; H, 4.54; N, 25.21;

Found: C, 69.96; H, 4.59; N, 25.44.

EXAMPLE 43

1-(2-Pyridyl)-4-(4-pyridyl)-pyrazole

By replacing 4-hydrazinopyridine hydrochloride employed in Example 41 with an equivalent quantity of 2-hydrazinopyridine hydrochloride there is obtained a 45% yield of 1-(2-pyridyl)-4-(4-pyridyl)-pyrazole which after recrystallization from di-isopropyl ether, melts at 109-111° C.

Analysis calculated for $C_{13}H_{10}N_4$:

C, 70.25; H, 4.54; N, 25.21;

Found: C, 70.23; H, 4.46; N, 24.90.

EXAMPLE 44

1-Amidino-5-amino-4-(4-pyridyl)-pyrazole

To 2-formyl-2-(4-pyridyl)-acetonitrile (7.3 g., 50 mmole) suspended in 1N hydrochloric acid (100 ml.) is added in small portions aminoguanidine bicarbonate (6.8 g., 50 mmole) and the mixture is heated on a steam bath for one hour. After a further 3 hours at room temperature the mixture is filtered and the filtrate made basic with 2N sodium hydroxide solution to give 4.0 g., (40%) of crude product, m.p. 179-181° C. Recrystallization of the crude product from ethyl acetate gives pure 1-amidino-5-amino-4-(4-pyridyl)-pyrazole, m.p. 185-186° C.

Analysis calculated for $C_9H_{10}N_6$:

C, 53.45; H, 4.98; N, 41.56;

Found: C, 53.26; H, 5.08; N, 41.81.

EXAMPLE 45

1-N-Methylthiocarbamoyl-4-(4-pyridyl)-pyrazole

A solution of 4-methylthiosemicarbazide (1.31 g., 12.5 mmole) in water (13 ml.) is added to a warm solution of 4-pyridylmalondialdehyde (1.49 g., 10 mmole) in methanol (150 ml.) containing a few drops of acetic acid. The mixture is heated under reflux for 6 hours, cooled and the solid collected yielding 924 mg. (42%) of product, m.p. 170-172° C. Recrystallization from aqueous methanol provides product in the form of colorless needles, m.p. 172-173.5° C.

Analysis calculated for $C_{10}H_{10}N_4S$:

C, 55.03; H, 4.62; N, 25.67; S, 14.69;

Found: C, 55.23; H, 4.63; N, 25.40; S, 14.72.

EXAMPLE 46

1-Propargyl-4-(4-pyridyl)-pyrazole hydrochloride monohydrate

4-(4-Pyridyl)-pyrazole (2.90 g., 20 mmole) is added to a solution of sodium (460 mg., 20 mmole) in dry ethanol (30 ml.), and then propargyl bromide (2.38 g., 20 mmole) is added. The mixture is stirred at room temperature for 48 hours and evaporated in a rotary evaporator. The residue is partitioned between ether and dilute sodium hydroxide solution thereby removing unreacted pyridyl-pyrazole from the ether solution. Evaporation of the dried (over magnesium sulfate) ethereal solution affords 1.4 g. of oil which is dissolved in isopropanol and a slight excess of ethanolic hydrogen chloride is added to precipitate the hydrochloride of the product. The crude salt on recrystallization from a mixture of methanol and isopropanol affords 1.4 g. (29.5%) of product, m.p. 203-205° C.

Analysis calculated for $C_{11}H_9N_3 \cdot HCl \cdot H_2O$:

C, 55.58; H, 5.08; Cl, 14.91; N, 17.67;

Found: C, 55.71; H, 5.12; Cl, 14.65; N, 17.60.

EXAMPLE 47

5-Amino-1-ethoxycarbonylmethyl-4-(4-pyridyl)-pyrazole hydrochloride

A mixture of 2-formyl-(4-pyridyl)-acetonitrile (2.98 g., 20 mmole), ethylhydrazinoacetate hydrochloride (4.0 g., 26 mmole), sodium acetate trihydrate (3.50 g., 26 mmole), acetic acid (3.5 ml.) and benzene (80 ml.) is stirred under reflux under a Dean-Stark trap for 4 hours by which time 2.2 ml. of water is collected. Some unreacted cyano aldehyde remains unreacted and therefore more ethylhydrazinoacetate hydrochloride (1.0 g., 6.5 mmole) and sodium acetate trihydrate (900 mg., 6.5 mmole) is added and the

mixture heated for an additional 6 hours. A further 6.5 mmole of each of the two compounds is added and the mixture is heated overnight. The benzene is evaporated under reduced pressure and the residue is extracted with boiling isopropanol. Treatment of the filtrate with ethanolic hydrogen chloride precipitates the hydrochloride of the product and more is obtained by addition of a little dry ether providing a total yield of 2.4 g. (42%), m.p. 210-215° C. (dec.). Recrystallization of the salt from absolute ethanol affords pure compound, m.p. 227-229° C. (dec.).

Analysis calculated for $C_{12}H_{14}N_4O_2 \cdot HCl$:

C, 50.98; H, 5.35; Cl, 12.54; N, 19.81;

Found: C, 50.66; H, 5.47; Cl, 12.62; N, 19.94.

EXAMPLE 48

1-Methyl-4-(4-pyridyl)-5-(1-pyrrolyl)-pyrazole hydrochloride

A mixture of 1-methyl-4-(4-pyridyl)-5-amino-pyrazole (1.74 g., 10 mmole), prepared as described in Example 6, 2,5-dimethoxy-tetrahydrofuran (1.32 g., 10 mmole) and acetic acid (10 ml.) is heated on a steam bath for 30 minutes and then under reflux in an oil bath for 30 minutes. The acetic acid is distilled off under vacuum and the residue is dissolved in isopropanol (20 ml.) and a slight excess of ethanolic hydrogen chloride solution is added to afford 2.39 g. of the hydrochloride of the product, m.p. ca. 275-285° C. The solid sublimes readily above about 240° C. Purification can be effected by recrystallization from 1:1 ethanol/isopropanol from which the compound separates in glistening crystals, m.p. 285-287° C. with marked sublimation.

Analysis calculated for $C_{13}H_{12}N_4 \cdot HCl$:

C, 59.89; H, 5.03; Cl, 13.60; N, 21.49;

Found: C, 59.56; H, 5.22; Cl, 13.36; N, 21.71.

EXAMPLE 49

1-(2-Dimethylaminoethyl)-4-(4-pyridyl)-5-amino-pyrazole hydrochloride

A mixture of 2-formyl-2-(4-pyridyl)-acetonitrile (1.46 g., 10 mmole), 2-dimethylaminoethylhydrazine (1.34 g., 13 mmole), benzene (40 ml.) and acetic acid (1.5 ml.) is heated under reflux overnight. Evaporation of the solvent yields an oil, which is dissolved in water. The solution is made basic with 10N sodium hydroxide solution (3 ml.). Continuous extraction with methylene chloride provides the free base as an oil (1.2 g.). The oil is dissolved in isopropanol and acidified with ethanolic hydrogen chloride thereby precipitating 950 mg. of the hydrochloride of the product which, following crystallization from a mixture of methanol and ether, yields 230 mg. of product, m.p. 293-295° C. (dec.).

$\int_{DSS}^{D_2O}$ NMR: ppm: 8.70 d(2H, J = 7 Hz, α-pyridyl proton); 8.23 s(1H, pyrazole proton); 8.16 d(2H, J = 7 Hz, β-pyridyl proton); 4.68 t(2H, J = 6.5 Hz, CH_2); 3.87 t(2H, J = 6.5 Hz, CH_2); 3.17 s(6H, 2 x CH_3).

EXAMPLE 50

1-(1-Methyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole dihydrochloride monohydrate

Step A: Preparation of 1-methyl-2-imidazolidinethione

N-Methylethylenediamine (37 g., 0.5 mole) in ether (80 ml.) is cooled to 10° C. in an ice bath and stirred vigorously while carbon disulfide (38 g.) in ether (30 ml.) is added dropwise. Stirring is continued for 30 minutes after addition is complete. The precipitate is removed by filtration, washed with ether and air-dried. The residue is heated

in an open flask immersed in an oil bath at 130° C. for two hours and the resulting residue recrystallized from hexane to give 25 g. (43%) yield of product, m.p. 126-128° C.

By replacing the N-methylethylenediamine by an equivalent quantity of N-ethyl-, N-propyl-, N-butyl-, N-pentyl- or other desired N-alkylethylenediamine the corresponding 1-alkyl-2-imidazolidinethione is obtained.

Step B: Preparation of 1-Methyl-2-methylthio-2-imidazoline hydriodide monohydrate

1-Methyl-2-imidazolidinethione (17.4 g., 0.15 mole) and methyl iodide (21.3 g., 0.15 mole) are refluxed in absolute ethanol (100 ml.) for a period of 2 hours. Upon cooling, the crystals that form are separated by filtration and air dried yielding 24 g. (62%) of compound, m.p. 96.5-98° C.

Analysis calculated for $C_5H_{10}N_2S \cdot HI \cdot H_2O$:

C, 21.75; H, 4.75; N, 10.15; I, 45.96;

Found: C, 22.16; H, 5.06; N, 10.41; I, 46.21.

Step C: Preparation of 1-Methyl-2-hydrazino-2-imidazoline hydriodide

1-Methyl-2-methylthio-2-imidazoline hydriodide (13 g., 0.05 mole) and hydrazine hydrate (5 g.) are reacted according to the procedure described in Example 37, Step A, to give 10.9 g. (89%) of compound, m.p. 180-182° C.

Analysis calculated for $C_4H_{10}N_4 \cdot HI$:

C, 19.85; H, 4.58; N, 23.15; I, 52.43;

Found: C, 20.12; H, 4.50; N, 22.89; I, 52.45.

Step D: Preparation of 1-(1-Methyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole dihydrochloride monohydrate

1-Methyl-2-hydrazino-2-imidazoline hydriodide (2.6 g., 10 mmole) and 4-pyridyl malondialdehyde (1.5 g., 10 mmole) in 2% hydrochloric acid (50 ml.) are reacted according to the procedure described in Example 37, Step B, to

give 1.83 g. (81%) of product, m.p. 68-70° C. The hydrochloride, prepared in the usual manner, melts at 257-260° C.

Analysis calculated for $C_{12}H_{13}N_5 \cdot 2HCl \cdot 2H_2O$:

C, 45.29; H, 5.38; N, 22.01; Cl, 22.28;

Found: C, 45.24; H, 5.45; N, 22.20; Cl, 22.28

EXAMPLE 51

1-(1-Ethyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole hydrochloride

Step A: Preparation of 1-Ethyl-2-methylthio-2-imidazoline hydriodide

1-Ethyl-2-imidazolidinethione (9 g., 0.07 mole) and methyl iodide (10 g., 0.07 mole) are refluxed in 100 ml. absolute ethanol for a period of 2 hours. Upon cooling the crystals that form are separated by filtration and air dried yielding 16.8 g. (88%) of 1-ethyl-2-methylthio-2-imidazoline hydriodide, m.p. 130.5-132° C.

Analysis calculated for $C_6H_{12}N_2S \cdot HI$:

C, 26.48; H, 4.81; N, 10.29; S, 11.78; I, 46.63;

Found: C, 26.29; H, 4.73; N, 10.39; S, 12.03; I, 47.01.

Step B: Preparation of 1-Ethyl-2-hydrazino-2-imidazoline hydriodide

1-Ethyl-2-methylthio-2-imidazoline hydriodide (15 g., 0.055 mole) and hydrazine hydrate (5 g.) are reacted according to the procedure described in Example 37, Step A, yielding 8.6 g. (61%) of product, m.p. 98-99° C.

Analysis calculated for $C_{15}H_{12}N_4 \cdot HI \cdot C_2H_5OH$:

N, 18.54; I, 42.00;

Found: N, 18.69; I, 42.52.

Step C: Preparation of 1-(1-Ethyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole dihydrochloride

1-Ethyl-2-hydrazino-2-imidazoline hydriodide (2.8 g., 11 mmole) and 4-pyridylmalondialdehyde (1.5 g., 10 mmole) in 2% hydrochloric acid (50 ml.) are reacted according to

the procedure described in Example 37, Step B, yielding 2.6 g. (93%) of product, m.p. 259-263° C.

Analysis calculated for $C_{13}H_{15}N_5 \cdot 2HCl$:

C, 49.69; H, 5.45; N, 22.29; Cl, 22.57;

Found: C, 49.83; H, 5.80; N, 22.28; Cl, 22.48.

By following the procedure described in Example 50, Steps A-D, with the exception the N-methylethylenediamine is replaced by an equivalent quantity of

N-n-propylethylenediamine (Example 52),

N-isopropylethylenediamine (Example 53) and

N-(2-butyl)ethylenediamine (Example 54),

there is obtained, respectively:

EXAMPLE 52

1-(1-n-Propyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole dihydrochloride

Step A: Preparation of 1-n-Propyl-2-imidazolidinethione

Yield, 85%; m.p. 88-89° C.

Analysis calculated for $C_6H_{12}N_2S$:

C, 49.96; H, 8.39; N, 19.42; S, 22.23;

Found: C, 49.95; H, 8.38; N, 19.69; S, 21.97.

Step B: Preparation of 1-n-Propyl-2-methylthio-2-imidazoline hydriodide

Yield 82%; m.p. 118-121° C.

Analysis calculated for $C_7H_{14}N_2S \cdot HI$:

C, 29.38; H, 5.28; N, 9.79; S, 11.20; I, 44.34;

Found: C, 29.85; H, 5.04; N, 10.00; S, 11.50; I, 44.22.

Step C: Preparation of 1-n-Propyl-2-hydrazino-2-imidazoline hydriodide

Yield 87%; m.p. 102° C.

NMR: ppm: 4.72 (2H, imidazoline protons); 3.18 t(2H, CH_2, J = 7 Hz); 2.65 sextuplet (2H, CH_2, J = 7 Hz); 0.88 t(3H, CH_3, J = 7 Hz).

Step D: Preparation of 1-(1-n-Propyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole dihydrochloride

Yield 40%; m.p. 234-237° C. (dec.).

Analysis calculated for $C_{14}H_{17}N_5 \cdot 2HCl$:

C, 51.23; H, 5.83; N, 21.34; Cl, 21.60;

Found: C, 51.49; H, 5.63; N, 21.61; Cl, 21.70.

EXAMPLE 53

1-(1-Isopropyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole dihydrochloride

Step A: Preparation of 1-Isopropyl-2-imidazolidinethione

Yield, 55%; m.p. 165-166° C.

Analysis calculated for $C_6H_{12}N_2S$:

C, 49.96; H, 8.39; N, 19.42; S, 22.23;

Found: C, 49.85; H, 8.45; N, 19.62; S, 22.40.

Step B: Preparation of 1-Isopropyl-2-methylthio-2-imidazoline hydriodide

Yield, 83%; m.p. 139-141° C.

Analysis calculated for $C_7H_{14}N_2S \cdot HI$:

C, 29.38; H, 5.28; N, 9.79; S, 11.20; I, 44.34;

Found: C, 29.82; H, 5.12; N, 9.87; S, 11.43; I, 44.23.

Step C: Preparation of 1-Isopropyl-2-hydrazino-2-imidazoline hydriodide

Yield, 90%; m.p. 48-57° C.

NMR: ppm: 3.80 septuplet(1H, CH, J = 6 Hz); 3.75 (2H, imidazoline protons); 1.22 d(3H, CH_3, J = 6 Hz).

Step D: Preparation of 1-(1-Isopropyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole dihydrochloride

Yield 45%; m.p. 256-258° C. (dec.).

Analysis calculated for $C_{14}H_{17}N_5 \cdot 2HCl$:

C, 51.23; H, 5.83; N, 21.34; Cl, 21.60;

Found: C, 51.45; H, 5.86; N, 21.71; Cl, 21.25.

EXAMPLE 54

1-[1-(2-Butyl)-2-imidazolin-2-yl]-4-(4-pyridyl)-pyrazole dihydrochloride

Step A: Preparation of 1-(2-Butyl)-2-imidazolidinethione

Yield, 65%; m.p. 155-156° C.

Analysis calculated for $C_7H_{14}N_2S$:

C, 53.12; H, 8.92; N, 17.70; S, 20.26;

Found: C, 52.96; H, 8.69; N, 18.00; S, 20.37.

Step B: Preparation of 1-(2-Butyl)-2-methylthio-2-imidazoline hydriodide

Yield, 86%; m.p. 110-112° C.

Analysis calculated for $C_8H_{16}N_2S \cdot HI$:

C, 32.01; H, 5.70; N, 9.33; S, 10.68; I, 42.27;

Found: C, 31.83; H, 5.46; N, 9.51; S, 10.98; I, 42.53.

Step C: Preparation of 1-(2-Butyl)-2-hydrazino-2-imidazoline hydriodide

Yield, 85%; as thick yellow oil.

NMR: ppm: 3.70 (2H, imidazoline protons); 3.60 sextuplet (2H, CH, J = 7 Hz); 1.65 quintuplet (2H, CH_2, J = 7 Hz); 1.20 d(3H, CH_3, J = 7 Hz); 0.85 t(3H, CH_3, J = 7 Hz).

Step D: Preparation of 1-[1-(2-Butyl)-2-imidazolin-2-yl]-4-(4-pyridyl)-pyrazole dihydrochloride

Yield, 28%, m.p. 257-259° C.

Analysis calculated for $C_{15}H_{19}N_5 \cdot 2HCl$:

C, 52.63; H, 6.18; N, 20.46; Cl, 20.72;

Found: C, 52.51; H, 6.38; N, 20.47; Cl, 20.61.

EXAMPLE 55

1-Methyl-5-phenyl-4-(4-pyridyl)-pyrazole

To a mixture of 1-methyl-4-(4-pyridyl)-5-aminopyrazole (870 mg., 5 mmole), (Example 6 product) acetic anhydride (1.53 g., 15 mmole), anhydrous potassium acetate (500 mg., 5.1 mmole) and benzene (15 ml.) stirred under

reflux is added dropwise over one hour a solution of isoamyl nitrite (1.0 ml., 880 mg., 7.5 mmole) in benzene (5 ml.). The mixture is heated under reflux for 22 hours, cooled to room temperature and diluted with more benzene (15 ml.). Chromatographic grade silica gel (4 g.) is added and the solvent is evaporated under reduced pressure. The residue is placed at the top of a column of silica gel (80 g.) and developed by the dry column technique with ethyl acetate. After a small two component eluate, the product is collected. Evaporation of the solution affords 522 mg. (42%) of brown oil, which soon solidifies. Recrystallization of the crude base from di-isopropyl ether (charcoal) gives the product in the form of colorless needles, m.p. 129-129.5° C.

Analysis calculated for $C_{15}H_{13}N_3$:

C, 76.57; H, 5.57; N, 17.86;

Found: C, 76.60; H, 5.62; N, 18.02.

EXAMPLE 56

1-Methyl-4-(4-pyridyl)-5-(2-furyl)-pyrazole

Replacing benzene in Example 55 with furan as solvent and reactant and following substantially the same procedure there is obtained 1-methyl-4-(4-pyridyl)-5-(2-furyl)-pyrazole which can be isolated by chromatography and purified by recrystallization from di-isopropyl ether.

EXAMPLE 57

1-(1-Ethyl-2-imidazolin-2-yl)-3-methyl-4-(4-pyridyl)-5-amino-pyrazole

By replacing, in Example 44, aminoguanidine bicarbonate with an equimolecular quantity of 1-ethyl-2-hydrazino-2-imidazoline hydriodide and replacing 2-formyl-2-(4-pyridyl)-acetonitrile with an equimolecular amount of 2-acetyl-2-(4-pyridyl)-acetonitrile and using 100 ml. of 0.5N hydrochloric acid in place of 100 ml. of 1N hydrochloric acid,

there is obtained 1-(1-ethyl-2-imidazolin-2-yl)-3-methyl-4-(4-pyridyl)-5-amino-pyrazole.

EXAMPLE 58

1,3-Dimethyl-4-(4-pyridyl)-5-amino-pyrazole

By replacing 2-formyl-2-(4-pyridyl)-acetonitrile in Example 6 with an equivalent amount of 2-acetyl-2-(4-pyridyl)-acetonitrile there is obtained 1,3-dimethyl-4-(4-pyridyl)-5-amino-pyrazole which is isolated as the hydrochloride salt and purified by recrystallization from ethanol.

EXAMPLE 59

1,3-Dimethyl-4-(4-pyridyl)-5-(1-pyrrolyl)-pyrazole

By replacing 1-methyl-4-(4-pyridyl)-5-amino-pyrazole in Example 55 with 1,3-dimethyl-4-(4-pyridyl)-5-amino-pyrazole (Example 58 product) there is obtained 1,3-dimethyl-4-(4-pyridyl)-5-(1-pyrrolyl)-pyrazole conveniently isolated as the hydrochloride salt and purified by recrystallization from isopropanol.

EXAMPLE 60

1-(1-Ethyl-2-imidazolin-2-yl)-4-(4-pyridyl)-5-amino-pyrazole maleate

A mixture of 1-ethyl-2-hydrazino-2-imidazoline hydriodide (3.05 g., 11.8 mmole), 2-formyl-2-(4-pyridyl)-acetonitrile (1.73 g., 11.8 mmole) and N hydrochloric acid (11.8 ml.) is warmed on a steam bath with stirring until a solution is obtained. The solution is allowed to stand at ambient temperature for 4 hours, then it is made basic with 5N sodium hydroxide solution and extracted with ethyl acetate (3 x 19 ml.). The extract is washed with a little saturated sodium chloride solution, dried over magnesium sulfate and evaporated to a reddish-brown oil, 2.95 g. (97%).

The oil is treated with hot isopropanol (five parts volume by weight) containing an equimolar amount of maleic acid. When cool, the solid is collected and washed with a little isopropanol to afford 80% of 1-(1-ethyl-2-imidazolin-2-yl)-4-(4-pyridyl)-5-amino-pyrazole hydrogen maleate, m.p. 142-145° C. (dec.).

Analysis calculated for $C_{13}H_{16}N_6 \cdot C_4H_4O_4$:

C, 52.30; H, 5.68; N, 21.53;

Found: C, 52.52; H, 5.35; N, 21.18.

EXAMPLE 61

1-Methyl-4-(4-pyridyl)-5-(2,5-dimethylpyrrol-1-yl)-pyrazole hydrochloride

Replacement of 2,5-dimethoxy-tetrahydrofuran in Example 48 with an equivalent amount of 2,5-hexanedione and extending the heating under reflux from 30 to 90 minutes affords 47% of 1-methyl-4-(4-pyridyl)-5-(2,5-dimethylpyrrol-1-yl)-pyrazole hydrochloride after the appropriate work-up as described in Example 48. The compound crystallizes from isopropanol in pale cream needles, m.p. 259-261° C. (dec.).

Analysis calculated for $C_{15}H_{16}N_4 \cdot HCl$:

C, 62.39; H, 5.93; Cl, 12.28; N, 19.40;

Found: C, 62.63; H, 5.61; Cl, 12.17; N, 19.70.

EXAMPLE 62

1-Methyl-4-(4-pyridyl)-5-ethylamino-pyrazole hydrochloride

To a slurry of lithium aluminum hydride (1.28 g., 34 mmole) in tetrahydrofuran (70 ml.) under dry nitrogen is added 1-methyl-4-(4-pyridyl)-5-acetamido-pyrazole (Example 11) (4.9 g., 22.5 mmole) in small portions and with stirring. Then the mixture is stirred at 45-50° C. for 3 hours, and cooled to ambient temperature. Excess hydride is decomposed by the successive addition of water (1.3 ml.), 10%

sodium hydroxide solution (1.95 ml.) and water (3.4 ml.). The metal hydroxides are filtered off and the filtrate evaporated to an oil. Additional product is obtained by dissolving the solids in 5N sodium hydroxide solution and extracting the solution with ether. The combined crude base is dissolved in isopropanol and a slight excess of ethanolic hydrogen chloride solution added to give 1-methyl-4-(4-pyridyl)-5-ethylamino-pyrazole hydrochloride, 1.95 g. (36%), m.p. 257-260° C. Following recrystallization from isopropanol the product has m.p. 258-261° C.

Analysis calculated for $C_{11}H_{14}N_4 \cdot HCl$:

C, 55.34; H, 6.33; Cl, 14.85; N, 23.47;

Found: C, 55.20; H, 6.22; Cl, 15.06; N, 23.60.

EXAMPLE 63

3(5)-Chloro-4-(4-pyridyl)-pyrazole

3(5)-Amino-4-(4-pyridyl)-pyrazole (1.60 g., 10 mmole) (Example 7 product) is suspended in 5N hydrochloric acid (10 ml.) and to the cooled suspension at 0-5° C. is added finely powdered sodium nitrite (690 mg., 10 mmole) in small portions and with stirring. The mixture is stirred at 0-5° C. for 30 minutes and then neutralized with 5N sodium hydroxide solution to afford 3(5)-chloro-4-(4-pyridyl)-pyrazole, 1.24 g. (69%). Recrystallization of the product from water gives analytically pure compound, m.p. 189-191° C.

Analysis calculated for $C_8H_6ClN_3$:

C, 53.49; H, 3.37; Cl, 19.74; N, 23.39;

Found: C, 53.27; H, 3.52; Cl, 19.72; N, 23.12.

EXAMPLE 64

1-(N,N-Dimethylamidino)-4-(4-pyridyl)-5-amino-pyrazole hydrochloride

To a suspension of 2-formyl-2-(4-pyridyl)-aceto-

nitrile (from Example 6) (12.4 g., 85 mmole) in N hydrochloric acid (85 ml.) is added dimethylaminoguanidine hydriodide (19.5 g., 85 mmole) and the mixture is heated at about 80° C. for one hour, then kept at ambient temperature for 3 hours, filtered and the filtrate made basic with 5N sodium hydroxide solution and immediately extracted with ethyl acetate (100 ml.). The aqueous phase is extracted with methylene chloride (5 x 100 ml.) affording 12 g. of crude oily 1-(N,N-dimethylamidino)-4-(4-pyridyl)-5-amino-pyrazole. The crude base is converted to a crystalline hydrochloride by dissolving the oil (2.3 g.) in isopropanol (30 ml.) and adding ethanolic hydrogen chloride solution. Melting point of hydrochloride, 205-206°C.

Analysis calculated for $C_{11}H_{14}N_6 \cdot HCl \cdot 1/2\ H_2O$:

C, 47.91; H, 5.85; Cl, 12.85; N, 30.47;

Found: C, 48.17; H, 5.46; Cl, 12.83; N, 30.60.

EXAMPLE 65

3-(4-Pyridyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrimidin-5-one

A mixture of 3(5)-amino-4-(4-pyridyl)-pyrazole, Example 7 product, (9.6 g., 60 mmole), ethyl acrylate (6.6 g., 66 mmole), triton B (40% solution of benzyl trimethylammonium hydroxide in methanol) (12 drops) and n-butanol (120 ml.) is heated under reflux for 3 days. On cooling the solution, 2.35 g. (18%) of 3-(4-pyridyl)-6,6-dihydro-4H-pyrazolo[1,5-a]pyrimidin-5-one, m.p. 268-270°, crystallizes out. Recrystallization of the product from alcohol raised the melting point to 270-272° C.

Analysis calculated for $C_{11}H_{10}N_4O$:

C, 61.67; H, 4.70; N, 26.15;

Found: C, 61.84; H, 5.00; N, 26.30.

EXAMPLE 66

3-(4-Pyridyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidine

To a slurry of lithium aluminum hydride (569 mg.,

15 mmole) in dry tetrahydrofuran (35 ml.) stirred under nitrogen is added 3-(4-pyridyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrimidin-5-one, Example 65 product, (2.78 g., 13 mmole) in small portions. The mixture is stirred under reflux overnight, then the excess hydride is destroyed by cautious addition of water (0.6 ml.), followed by 10% sodium hydroxide solution (1 ml.) and more water (1.7 ml.). The tetrahydrofuran solution is filtered and evaporated to afford 700 mg. of solid. More product is isolated by dissolving the metal hydroxides in 5N sodium hydroxide solution and extracting with methylene chloride providing an overall yield of 1.139 g. (43%). Recrystallization of the crude product from benzene gives pure compound, m.p. 166-168° C.

Analysis calculated for $C_{11}H_{12}N_4$:

C, 65.98; H, 6.04; N, 27.98;

Found: C, 65.83; H, 6.33; N, 27.53.

EXAMPLE 67

3-(4-Pyridyl)-4-methyl-4,5,6,7-tetrahydro-pyrazolo-[1,5-a]pyrimidine

A mixture of 3-(4-pyridyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidine, Example 66 product, (700 mg., 3.49 mmole), 98% formic acid (1 ml.), and formaldehyde solution (2 ml.) is heated under reflux for 24 hours. The mixture is evaporated to dryness and the residue treated with isopropanol (20 ml.). Addition of a slight excess of ethanolic hydrogen chloride solution causes the crystallization of 3-(4-pyridyl)-4-methyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidine hydrochloride, 485 mg., (65%). Recrystallization of the solid from ethanol (ca. 4 ml.) affords pure compound, m.p. 241-243° C.

Analysis calculated for $C_{12}H_{14}N_4 \cdot 2HCl$:

C, 50.18; H, 5.61; Cl, 24.69; N, 19.50;

Found: C, 50.45; H, 6.02; Cl, 24.66; N, 19.67.

EXAMPLE 68

3(5)-Methyl-4-(4-pyridyl)-pyrazole

Step A: Preparation of 4-Pyridylacetone

4-Picoline (93 g., 1 mole) is added to a suspension of sodium amide prepared from sodium (23 g., 1 mole) in 600 ml. anhydrous liquid ammonia. The mixture is stirred for 15 to 20 minutes. To the suspension of 4-picolyl, sodium ethyl acetate (66 g., 0.75 mole) is added over a period of 30 minutes and stirring continued for an extra hour. The reaction is quenched by addition of excess solid ammonium chloride and the liquid ammonia replaced by adding ether and warming on a water bath. When the ammonia evaporates, the reaction mixture is poured onto a mixture of ice and hydrochloric acid. The ether is decanted, the aqueous solution made basic and extracted with ether. The organic layer is washed with water, dried over magnesium sulfate and concentrated under vacuum, leaving a residue that is distilled at 70-75° C. at 1 mm. yielding 4-pyridyl acetone (5 g., 5%).

Step B: Preparation of 3(5)-Methyl-4-(4-pyridyl)-pyrazole

4-Pyridylacetone (135 mg., 1 mmole), ethyl formate (75 mg., 1 mmole), sodium ethoxide (100 mg., 1.5 mmole) are refluxed in benzene for 18 hours. The brownish solid is filtered off, dissolved in water, acidified with 10% hydrochloric acid and hydrazine hydrate is added (50 mg., 1 mmole). The solution is heated on the steam bath for 1 hour, then cooled to ambient temperature, made basic with 10% sodium hydroxide and extracted with ethyl acetate. The organic layer is washed with water until neutral and dried over magnesium sulfate. The evaporation of the solvent left 89 mg. of a yellow oil, identified as 3(5)-methyl-4-(4-pyridyl)-pyrazole by its NMR spectrum in dilute DCl.

NMR: ppm: 8.92 d(J = 6 Hz, α-pyridyl proton); 8.20 d(J = 6 Hz; β-pyridyl proton); 7.98 s(pyrazole proton); 2.45 s(CH_3).

EXAMPLE 69

3,5-Dimethyl-4-(4-pyridyl)-pyrazole

This product is obtained by replacing ethyl formate employed in Step B of Example 68 by an equivalent quantity of ethyl acetate and otherwise following substantially the same procedure.

Other 3,5-dialkyl-4-(4-pyridyl)-pyrazole compounds can similarly be prepared by employing the appropriate alkyl ester of an alkanoic acid.

EXAMPLE 70

1,3,5-Trimethyl-4-(4-pyridyl)-pyrazole

This product is prepared by replacing ethyl formate and hydrazine employed in Step B of Example 68 by equivalent quantities of ethyl acetate and methyl-hydrazine, respectively, and otherwise following substantially the same procedure.

Other 1-R^3-3,5-dialkyl-4-(4-pyridyl)-pyrazoles can similarly be prepared by employing the appropriate alkyl ester of an alkanoic acid and an H_2N-NHR^3 wherein R^3 is the desired 1-position substituent group.

EXAMPLE 71

1-(2-Imidazolin-2-yl)-3,5-dimethyl-4-(4-pyridyl)-pyrazole

This product is prepared by replacing ethyl formate and hydrazine employed in Step B of Example 68 by equivalent quantities of ethyl acetate and 2-imidazol-2-ylhydrazine, respectively, and otherwise following substantially the same procedure.

EXAMPLE 72

1,3(5)-Dimethyl-4-(4-pyridyl)-pyrazole

These compounds are prepared by replacing the hydrazine employed in Step B of Example 68 by an equivalent quantity of methyl-hydrazine and otherwise following substantially the same procedure.

EXAMPLE 73

1-Methyl-4-(4-pyridyl)-5-isopropoxy-pyrazole

A mixture of 1-methyl-4-(4-pyridyl)-5-hydroxy-pyrazole (prepared as described in Example 9) (10 mmole), sodium carbonate (11 mmole), isopropyl iodide (13.3 mmole) and sodium iodide in dimethylformamide (25 ml.) is heated at 55-60° C. for about 1/2 hour with stirring. The reaction mixture is quenched with water (ca. 150 ml.) and then extracted with 3 x 25 ml. ether. The ether extracts are combined, dired over magnesium sulfate and concentrated to dryness yielding 1-methyl-4-(4-pyridyl)-5-isopropoxy-pyrazole.

EXAMPLE 74

1-Methyl-4-(3-n-propoxy-4-pyridyl)-pyrazole

This product is prepared by replacing the 1-methyl-4-(4-pyridyl)-5-hydroxy-pyrazole and the isopropyl iodide employed in Example 73 by equivalent quantities of 1-methyl-4-(3-hydroxy-4-pyridyl)-pyrazole (prepared as described in Example 19) and n-propyl iodide, respectively, and otherwise following substantially the same procedure.

Other 4-(4-pyridyl)-5-alkoxy-pyrazoles and other 4-(3-alkoxy-4-pyridyl)-pyrazoles can be prepared by the methods described in Examples 73 and 74 by employing the appropriate alkyl halide.

Other known 4-(4-pyridyl)-pyrazole compounds that have been found to be effective bronchodilating agents in

the method of this invention are:

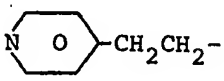
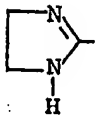
4-(4-pyridyl)-pyrazole and

1-carbamoyl-4-(4-pyridyl)-pyrazole.

The products of this invention were found, when tested according to standard protocols in anesthetized dogs, to inhibit bronchial constriction induced by one or more bronchoconstrictor agonists; known procedures for evaluating bronchodilating properties of products. In addition, certain compounds were also found to exhibit hypotensive properties, probably due to their actions as peripheral vasodilators, and are therefore of potential use as antihypertensive drugs.

The dose of representative products which was required to inhibit histamine induced bronchial constriction in anesthetized dogs at the ED_{50} level when tested by the above procedure is provided in the following table. It will be noted that the test data establishes that the compounds are generally more effective bronchial dilating agents than the control drug, theophylline. Because of this high order of activity, the active ingredients of the claimed method and formulations are useful in the management of asthma, allergic reactions and other disorders associated with or resulting from bronchial constriction.

TABLE I

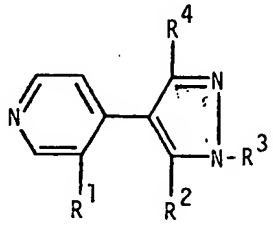
COMPOUND Structure I					ED_{50}
Ex. No.	R^1	R^2	R^3	R^4	mg./kg.
THEOPHYLLINE					64.5
12	H	$(CH_3)_2N-$	CH_3-	H	9.0
11	H	CH_3CONH-	CH_3-	H	50.0
4	H	H	$CH_2=CH-CH_2-$	H	13.0
24	H	H	$CH_3OCH_2CH_2-$	H	20.0
27	H	H		H	72.0
(p. 44)	H	H	H	H	9.0
35	H	H	$H_2N-C(=NH)-$	H	15.0
35	H	H	isethionate of above	H	15.0
3	H	H	$(CH_3)_2CHCH_2-$	H	14.0
37	H	H		H	10.0
31	H	H	$(CH_3)_2NCO-$	H	6.0 & 8.0
51	H	H		H	25.0

While the invention has been illustrated by certain specific members of the 4-(4-pyridyl)-pyrazole products made by certain specific methods and formulated into certain specific dosage forms, it is to be understood that the invention is not to be considered limited by or to the specific

embodiments illustrated but is to encompass other members of the products falling within the scope of the generic disclosure and claims as well as other methods or modifications of the methods described for their preparation, administration and formulations, all of which would be obvious in view of the teaching herein to one skilled in the art.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. The process for preparing a 4-(4-pyridyl)-pyrazole of the formula:

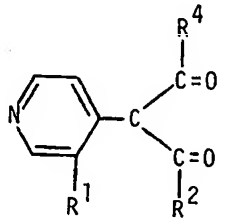


wherein R^1 represents hydrogen, nitro, amino, acetylamino, mono- or di-alkylamino, cyano, phenyl, hydroxy, alkoxy, or halo, preferably chloro; R^2 represents hydrogen, halogen, preferably chloro, alkyl, hydroxy, alkoxy, cyano, amino, acetylamino, mono- or di-alkylamino, phenyl, furyl, 4-pyridyl, 1-pyrrolyl or mono- or di-C_{1-3} alkyl-1-pyrrolyl; R^3 represents hydrogen, alkyl either straight or branched chain and having from 1-5 carbon atoms, alkenyl, alkinyl, C_{3-10} cycloalkyl, preferably adamantyl, haloalkyl, preferably polyfluoroalkyl, alkoxyalkyl, hydroxyalkyl, dialkylaminoalkyl, (4-pyridyl)-C_{1-3} alkyl, alkoxycarbonylalkyl, mono- or di-alkylaminocarbonyl-alkyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, 4-alkylpiperazinylcarbonyl, piperidinocarbonyl, N-alkylthio-carbamoyl, phenyl, amidino or mono- or di-alkyl substituted amidino, 2-imidazolin-2-yl or 1-C_{1-5} alkyl substituted 2-imidazolin-2-yl, 2-, 3- or 4-pyridyl, 2-(3,4,5,6-tetrahydro-pyrimidinyl), 2-(3,4-dihydro-1,3-thiazolyl), and 2-(5,6-dihydro-4(H)-1,3-thiazinyl); R^2 and R^3 can be linked together to form with the pyrazolo nucleus to which they are attached a 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl, a 4-C_{1-3} alkyl substituted 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl or a 6,7-dihydro-5(4H)-oxopyrazolo[1,5-a]pyrimidin-3-yl; and R^4

represents hydrogen and C_{1-3} alkyl, with the proviso that R^2, R^3 and R^4 are not hydrogen at the same time and that when R^3 is carbamoyl, R^2 and R^4 may not be hydrogen,

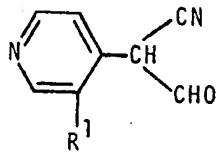
which comprises

A. when R^3 is other than NH_2: reacting a dicarbonyl compound of the formula:



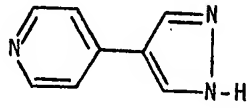
with a hydrazine of the formula H_2NNHR^3, wherein R^1, R^2, R^3 and R^4 are as previously defined; or

B. when R^3 is NH_2 and R^4 is hydrogen: reacting a 2-formyl-2-(4-pyridyl)acetonitrile of the formula:



with a hydrazine of the formula H_2NNHR^3, R^1 being as defined previously, and R^3 being defined as previously except that it is other than hydrogen; or

C. when R^3 is to be alkyl of 1 to 5 carbon atoms: alkylating a 4-(4-pyridyl)pyrazole of the formula:



with an alkyl halide.

2. The process of Step A of Claim 1, wherein 4-pyridylmalondialdehyde is reacted with methoxyethylhydrazine to form the 1-(2-methoxyethyl)-4-(4-pyridyl)pyrazole.

3. The process of Step A of Claim 1, wherein 4-pyridylmalondialdehyde is reacted with 4,4-dimethylsemicarbazide to form the 1-dimethylcarbamoyl-4-(4-pyridyl)-pyrazole.

4. The process of Step A of Claim 1, wherein 4-pyridylmalondialdehyde is reacted with aminoguanidine bicarbonate to form the 1-amidino-4-(4-pyridyl)pyrazole.

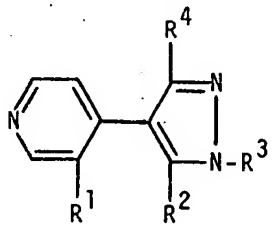
5. The process of Step A of Claim 1, wherein 4-pyridylmalondialdehyde is reacted with 1-ethyl-2-hydrazino-2-imidazoline to form the 1-(1-ethyl-2-imidazolin-2-yl)-4-(4-pyridyl)pyrazole.

6. The process of Step B of Claim 1, wherein 2-formyl-2-(4-pyridyl)acetonitrile is reacted with methyl hydrazine to form the 1-methyl-4-(4-pyridyl)-5-amino-pyrazole.

7. The process of Claim 6, comprising the further step of reacting the 1-methyl-4-(4-pyridyl)-5-amino-pyrazole with acetic anhydride to form the 1-methyl-4-(4-pyridyl)-5-acetamido-pyrazole.

8. The process of Claim 6, comprising the further step of reacting the 1-methyl-4-(4-pyridyl)-5-amino-pyrazole with a formaldehyde-formic acid mixture to form the 1-methyl-4-(4-pyridyl)-5-dimethylamino-pyrazole.

9. The 4-(4-pyridyl)pyrazole of the formula:



wherein R^1 represents hydrogen, nitro, amino, acetylamino, mono- or di-alkylamino, cyano, phenyl, hydroxy, alkoxy, or halo, preferably chloro; R^2 represents hydrogen, halogen, preferably chloro, alkyl, hydroxy, alkoxy, cyano, amino, acetylamino, mono- or di-alkylamino, phenyl, furyl, 4-pyridyl, 1-pyrrolyl or mono- or di-C_{1-3} alkyl-1-pyrrolyl; R^3 represents hydrogen, alkyl either straight or branched chain and having from 1-5 carbon atoms, alkenyl, alkinyl, C_{3-10} cycloalkyl, preferably adamantyl, haloalkyl, preferably polyfluoroalkyl, alkoxyalkyl, hydroxyalkyl, dialkylaminoalkyl, (4-pyridyl)-C_{1-3} alkyl, alkoxycarbonylalkyl, mono- or di-alkylaminocarbonyl-alkyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, 4-alkylpiperazinylcarbonyl, piperidinocarbonyl, N-alkylthio-carbamoyl, phenyl, amidino or mono- or di-alkyl substituted amidino, 2-imidazolin-2-yl or 1-C_{1-5} alkyl substituted 2-imidazolin-2-yl, 2-, 3- or 4-pyridyl, 2-(3,4,5,6-tetrahydro-pyrimidinyl), 2-(3,4-dihydro-1,3-thiazolyl), and 2-(5,6-dihydro-4(H)-1,3-thiazinyl); R^2 and R^3 can be linked together to form with the pyrazolo nucleus to which they are attached a 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl, a 4-C_{1-3} alkyl substituted 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl or a 6,7-dihydro-5(4H)-oxopyrazolo[1,5-a]pyrimidin-3-yl; and R^4 represents hydrogen and C_{1-3} alkyl, with the proviso that R^2, R^3 and R^4 are not hydrogen at the same time and that when R^3 is carbamoyl, R^2 and R^4 may not be hydrogen, when prepared by the process defined in Claim 1 or by an obvious chemical equivalent.

10. The 1-(2-methoxyethyl)-4-(4-pyridyl)pyrazole, when prepared by the process defined in Claim 2 or by an obvious chemical equivalent.

11. The 1-dimethylcarbamoyl-4-(4-pyridyl)pyrazole, when prepared by the process defined in Claim 3 or by an obvious chemical equivalent.

12. The 1-amidino-4-(4-pyridyl)pyrazole, when prepared by the process defined in Claim 4 or by an obvious chemical equivalent.

13. The 1-(1-ethyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole, when prepared by the process defined in Claim 5 or by an obvious chemical equivalent.

14. The 1-methyl-4-(4-pyridyl)-5-amino-pyrazole, when prepared by the process defined in Claim 6 or by an obvious chemical equivalent.

15. The 1-methyl-4-(4-pyridyl)-5-acetamido-pyrazole, when prepared by the process defined in Claim 7 or by an obvious chemical equivalent.

16. The 1-methyl-4-(4-pyridyl)-5-dimethylamino-pyrazole, when prepared by the process defined in Claim 8 or by an obvious chemical equivalent.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente